

**Penicillin Allergy Delabeling:
An Antibiotic Stewardship Initiative**

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Ask the Audience – Question #3

Which of the following is NOT commonly associated with penicillin allergy labels?

- A) Increased use of broad-spectrum antibiotics
- B) Longer hospital stays
- C) Fewer surgical site infections
- D) Increased readmission rates

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Ask the Audience – Question #1

Penicillin is the most common drug allergy label identified in medical records:

- A) True
- B) False

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Outline

- Background – penicillin allergy and clinical implications
- Types of hypersensitivity reactions to penicillin
- Identifying appropriate patients for penicillin allergy testing
- Steps in penicillin allergy testing
- Practical implementation of allergy delabeling

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Ask the Audience – Question #2

What percentage of patients with a penicillin allergy label are in fact tolerant to penicillin?

- A) <10%
- B) 25-30%
- C) 75-80%
- D) >90%

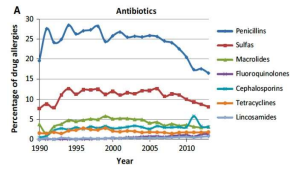
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Background – Penicillin Allergy

- 10-20% of patients carry a diagnosis of penicillin allergy
- Most commonly reported drug allergy
- Many patients given a penicillin allergy label in childhood
 - 75% of pediatric penicillin allergy labels acquired before 3 years of age
- Most patients do not undergo evaluation to determine accuracy or persistence of penicillin allergy



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Zhou et al. Allergy 2016

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Penicillin Allergy – The Reality

A penicillin-allergy label is usually acquired in childhood

Up to 20% of the population engaged in medical care is labeled as penicillin-allergic

Formal Allergy Assessment

<math>< 3\%</math> Labeled as allergic to penicillin are truly allergic.

>90% of patients with an allergy label may in fact tolerate penicillin

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Clinical Implications of a Penicillin Allergy Label

Health Implications

- Personal**
 - 1) Increased use of broad-spectrum antibiotics (vancomycin, fluoroquinolones, clindamycin)
 - 2) Higher rates of nosocomial infections (MRSA, VRE, and *C difficile*)
 - 3) Greater drug-induced toxicity
 - 4) More perioperative surgical site infections
 - 5) Increased all-cause mortality
- Population**
 - 1) Increased antibiotic resistance
 - 2) Prolonged hospitalizations
 - 3) Increased readmission rates
 - 4) Greater health care costs

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Reasons for False Penicillin Allergy Labels

- Labels often represent self-reported allergy
 - Family history
 - Expected adverse effect (headache, GI upset, etc.)
- Initial misdiagnosis
 - Viral exanthem
 - Interaction between pathogen and antibiotic
- Waning sensitivity over time
 - Every year, ~10% of penicillin-allergic patients lose their sensitivity

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Support for Penicillin Allergy Delabeling

AAAAI
American Academy of Allergy Asthma & Immunology

"Penicillin allergy evaluation should be performed proactively in patients with a penicillin allergy label"

Choosing Wisely
An initiative of the ABIM Foundation

"By identifying the overwhelming majority of individuals who can safely receive penicillin and penicillin-like drugs, we can improve the appropriateness of antibiotic therapy and clinical care outcomes"

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

"Before prescribing broad-spectrum antibiotics to a patient thought to be penicillin-allergic, evaluate the patient for true penicillin allergy (IgE-mediated) by conducting a history and physical, and, when appropriate, a skin test and challenge dose"

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<https://www.aaaai.org/pubs/afp/collections/choosing-wisely/157.html>
<https://www.cdc.gov/antibiotic-use/choosing-wisely/penicillin-allergy.html>

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Hypersensitivity Reactions to Penicillin

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Reactions to Penicillin

- Antibody-Mediated:
 - Type I, Immediate Hypersensitivity (IgE-mediated)
 - Penicillin hapten-carrier complex (first exposure)
 - Dendritic cell (MHC-II) → Naive T cell (TCR) → TH2 cell (Interleukin-4)
 - Naive T cell → B cell (Interleukin-4, Interleukin-13) → Plasma cell
 - Plasma cell → IgE antibodies
 - IgE antibodies → Mast cell → IgE cross-linking and degranulation → Penicillin hapten-carrier complex (second exposure)
 - Clinical Phenotype: **Allergic Reaction:** Urticaria, Angioedema, Bronchospasm, Cardiovascular collapse, Anaphylaxis
 - Type II, Cytotoxic reaction → hemolytic anemia, thrombocytopenia
 - Type III, Immune Complex reaction → small-vessel vasculitis, serum sickness
- T-cell Mediated

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Cutaneous Drug Reactions

IgE-mediated reactions Onset: minutes to hours into treatment course Raised off of the skin Pruritic Each lesion lasts <24 h Fades without scarring	Benign T-cell-mediated reactions Onset: days into treatment course Typically less pruritic than IgE-mediated reactions Each lesion lasts >24 h Free re-exposure with resolution over days to weeks	Severe T-cell-mediated reactions or severe cutaneous adverse reactions Onset: days to weeks into treatment course Blistering and/or skin discoloration Medical and/or organ involvement Usually requires hospitalization
		
		
		

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NIAID/FAAN Anaphylaxis Criteria

1 Acute onset of an illness (minutes to several hours) with involvement of: <ul style="list-style-type: none"> Skin and/or mucosa <ul style="list-style-type: none"> Pruritus Flushing Hives Angioedema And either Respiratory compromise <ul style="list-style-type: none"> Dyspnea Wheeze-bronchospasm Peak expiratory flow ↓ Stridor Hypoxemia Or BP or end-organ dysfunction <ul style="list-style-type: none"> Collapse Syncope Incontinence 	2 or more of the following that occur rapidly after exposure to a likely allergen for that patient: <ul style="list-style-type: none"> Skin and/or mucosa <ul style="list-style-type: none"> Pruritus Flushing Hives Angioedema Respiratory compromise <ul style="list-style-type: none"> Dyspnea Wheeze-bronchospasm Peak expiratory flow ↓ Stridor Hypoxemia BP or end-organ dysfunction <ul style="list-style-type: none"> Collapse Syncope Incontinence Persistent GI Symptoms <ul style="list-style-type: none"> Vomiting Crampy Abdominal Pain Diarrhea 	3 After exposure to known allergen for that patient (minutes to several hours): <ul style="list-style-type: none"> BP
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Cedars Sinai | Mahaveen V, Decker WW, Sheel LG, Li JT, Campbell RL. Visual representation of National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria for anaphylaxis. Int J Emerg Med. 2009 | 14

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How Common Are Penicillin Reactions?

- Possible hypersensitivity reactions occur with 0.5% to 2.0% of penicillin administrations
- BUT Penicillin-associated anaphylaxis is very rare
 - 1 in 255,000 oral exposures
 - 1 in 124,000 parenteral exposures
- Rate of IgE-mediated reactions to penicillin has been decreasing over time
 - Positive skin tests decreased from 15% (1995) → 3% (2007) → 0.8% (2013)

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Reactions to Penicillin

- Antibody-Mediated
- T-cell Mediated:
 - Antigen-presenting cell → Penicillin hapten-carrier complex → CD4+ or CD8+ cell (TCR) → TH1 cell (Interleukin-2, Interleukin-13) → T cell
 - TH1 cell → Interleukin-4, Interleukin-5, Interleukin-9 → Eosinophil → **DRESS, 2-to-8-week delay:** Epidermal edema, fever, lymphadenopathy, eosinophilia, atypical lymphocytosis, and infiltration of skin and internal organs
 - TH1 cell → Granulysin → Perforin → **SJS-TEN, 4-to-28-day delay:** Epidermal necrosis, subepidermal bullae, and involvement of multiple mucous membranes
 - TH1 cell → Interleukin-3 → Neutrophil → **AGEP, 24-to-48-hour delay:** Fever, neutrophilic leukocytosis, sterile pustules in stratum corneum and epidermis, dermal edema, and infiltration of neutrophils, CD4+ T cells, CD8+ T cells, and some eosinophils
 - Benign cutaneous exanthems
 - Severe cutaneous adverse reactions (SCARs): Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson's Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP)

Cedars Sinai | Castells et al Penicillin Allergy. NEJM 2019 | 15

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Ask the Audience – Question #4

All patients with a penicillin allergy label must undergo skin testing to have their allergy label removed:

A) True
B) False

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Ask the Audience – Question #5

The reaction caused by a positive penicillin skin test is referred to as which of the following?

- A) "lump or bump"
- B) "bleb and blister"
- C) "wheal and flare"
- D) "hit or miss"

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Drug Allergy History

- How long ago did the reaction occur?
- Was this your first course of penicillin or had you taken it before?
- What were the reaction symptoms?
- What was the time course?
 - How long after taking medication did the reaction occur?
 - How long did symptoms last?
 - Did the reaction occur after 1st dose or multiple days into a course?
- What treatment was required?
- Was there any blistering rash, desquamation, mucosal involvement, fever, joint pain, hepatitis, nephritis, or hemolytic anemia?

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Ask the Audience – Question #6

Which of the following patients should NOT undergo penicillin allergy testing:

- A) A 17 year old male who developed isolated lip swelling during a course of penicillin
- B) A 46 year old male with a history of penicillin-induced Stevens-Johnson syndrome
- C) A 10 year old female with a history of mild rash after amoxicillin at age 2
- D) A 68 year of female with a history of mild rash after amoxicillin at age 2

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Penicillin Allergy Evaluation

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Drug Allergy History

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Contraindications to Delabeling

- SCAR
 - Drug reaction with eosinophilia and systemic symptoms (DRESS)
 - Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN)
 - Acute generalized exanthematous pustulosis (AGEP)
- Organ-Specific Injury
 - Drug-induced liver injury
 - Acute interstitial nephritis
- Hemolytic anemia, thrombocytopenia




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Drug Allergy History


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Risk Stratification


Low Risk	<ol style="list-style-type: none"> 1) Isolated non-allergic symptoms (headache, diarrhea) 2) Family history of penicillin allergy 3) Pruritus without rash 4) Unknown/remote (>5 yrs) reaction without IgE-type symptoms
Moderate Risk	<ol style="list-style-type: none"> 1) Urticaria (or other pruritic rashes) 2) Reactions with features of IgE-mediated symptoms (but not anaphylaxis)
High Risk	<ol style="list-style-type: none"> 1) History of anaphylaxis 2) History of positive penicillin skin testing 3) Recurrent penicillin reactions 4) Hypersensitivities to multiple beta-lactam antibiotics

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Drug Allergy History


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Options for Penicillin Allergy Delabeling

- 1) History alone
- 2) Direct Oral Challenge
- 3) Skin testing + Oral Challenge



Risk Level

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Delabeling Based on History Alone

- ~20% of penicillin allergies can be delabeled based on history alone
 - Family history
 - Intolerance (fatigue, headache, chills, isolated GI upset)
 - Documented tolerance to penicillin subsequent to the last reported reaction
- Additional testing can be considered in anxious or hesitant patients



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PEN-FAST Clinical Decision Rule

PEN	Penicillin allergy reported by patient	<input type="checkbox"/>	If yes, proceed with assessment
F	Five years or less since reaction ^a	<input type="checkbox"/>	2 points
A	Anaphylaxis or angioedema or	<input type="checkbox"/>	2 points
S	Severe cutaneous adverse reaction ^b	<input type="checkbox"/>	1 point
T	Treatment required for reaction ^c	<input type="checkbox"/>	Total points

Interpretation	
0	Very low risk of positive penicillin allergy test <1% (<1 in 100 patients reporting penicillin allergy)
1-2	Low risk of positive penicillin allergy test 5% (1 in 20 patients)
3	Moderate risk of positive penicillin allergy test 20% (1 in 5 patients)
4-5	High risk of positive penicillin allergy test 50% (1 in 2 patients)

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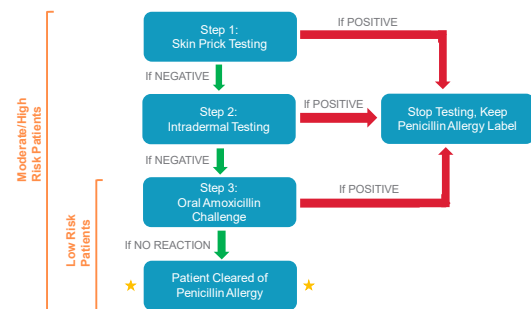
Penicillin Allergy Delabeling – Oral Amoxicillin Challenge

- Age-appropriate dose (typically 125-500mg amoxicillin)
 - Single dose or 2-step graded challenge
 - Example of graded challenge: 10% followed by 90%
- 1 hour monitoring period
 - Signs/symptoms of anaphylaxis
 - Appropriate reaction treatment: IM epinephrine, inhaled bronchodilators, antihistamines, corticosteroids
- If no reaction → patient can be successfully delabeled
 - Benign morbilliform rashes occurs in 1% to 3% of delabeled patients with next full penicillin course



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Delabeling Based on Skin Testing and Oral Challenge



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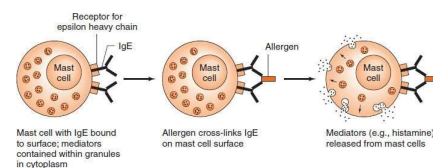
Delabeling Based on Direct Amoxicillin Challenge

- Appropriate for low risk patients
 - Remote (> 5 years ago) reaction history of cutaneous-only symptoms
 - Hesitant to be delabeled based on history alone
- Low reaction rate of 4-10%
- Recommended approach in pediatric patients with benign cutaneous reaction histories
- Also shown to be safe in low risk adults
 - PEN-FAST is a validated tool to help risk stratification of adult patients
 - Score <3 associated with low risk of severe penicillin allergy

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Skin Testing – How Does It Work?

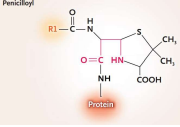
- Detects penicillin-specific IgE
- Allergen encounters cutaneous mast cells → penicillin-specific IgE becomes cross-linked on mast cell surfaces → mast cell degranulation and "wheal and flare" reaction



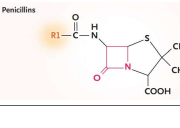
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Skin Testing Reagents

- 1) Positive (histamine) and negative (saline) controls
- 2) Major determinant: penicilloyl polylysine (PRE-PEN)



Penicilloyl
- 3) Minor determinant: benzyl penicillin (PEN-G)




Penicillins

Cabrillo et al NEJM 2019 37

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Accuracy and Implications of Penicillin Testing

- Negative predictive value of skin testing is >95% and approaches 100% when combined with oral amoxicillin challenge
- Delabeling allows future use of penicillin antibiotics (including aminopenicillins)



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Skin Testing – What Does It Look Like?

- Total time required: 45 min - 1 hour
- Skin prick test: read after 15min
 - Positive response: wheal \geq 3mm compared to negative control
- Intradermal test: read after 15-20min
 - Positive response: wheal \geq 3mm compared to negative control



Skin Prick Test



Intradermal Test



Negative Skin Prick Result



Positive Intradermal Result

Shanoy et al JAMA 2019 38

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Other Important Steps in Allergy Delabeling

- Appropriate testing documentation
- EHR alert
- Removal of allergy label from chart
- Wallet card
- Patient education

I am NOT allergic to Penicillin

Penicillin skin testing (prick and intradermal) followed by an oral Amoxicillin challenge was performed at Parkland on _____

RESULT: Negative (No Reaction)

Test performed by _____

ALLERGY INFORMATION

Name: _____

Date of birth: _____

Allergies: _____ Reaction: _____

Cedars Sinai Lofthol et al J Allergy Clin Immunol Pract 2021 41

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Sample Recording Form for Penicillin Skin Testing

Reagent	Skin Prick Test		Intradermal Test	
	Wheal (mm)	Flare (mm)	Wheal (mm)	Flare (mm)
Saline (negative control)				
Histamine (positive control)				
Penicilloyl Polylysine (PRE-PEN)				
Penicillin G (PEN-G)				

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Practical Implementation of Penicillin Allergy Delabeling

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Who Performs Penicillin Allergy Testing?

- Health care providers with appropriate education and training
 - Allergy specialists (including trainees)
 - Infectious disease specialists (including trainees)
 - Advance practice providers
 - Pharmacists
 - Nurses
- Regulations vary by state
- The majority of US hospitals lack sufficient resources to address penicillin allergies
 - 2020 study of 121 hospitals from 38 US states showed that only 44% had access to an allergist for consults and 39% had access to penicillin skin testing

Cedars Sinai | Mancini et al. Clin Infect Dis 2020 43

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Implementation of Penicillin Allergy Testing – Resources Required

Evaluation				
Drug Allergy History	Skin Testing (if indicated)	Drug Challenge	Counseling and Documentation	Reaction Management
Education and training Standard history form	Education and training Testing protocol Testing reagents Testing space Preparation time Administration time	Education and training Administration protocol Medications Testing space Observation protocol	Education and training EHR access	Education and training Emergency medications Treatment protocol Plan for escalation of care Treatment time

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Where is Penicillin Allergy Testing Performed?

Cedars Sinai | Samarakoon et al Ann Allergy Asthma Immunol 2023 44

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Pharmacist-Driven Penicillin Testing

- First pharmacy-driven program reported in 2004 (Iowa)
- Various models exist
- Barriers include training, scope of practice, billing, resources

Primary Population	State/Country	PST Model
Multicenter (1 academic teaching hospital and 2 community hospitals) [3]	Canada	Allergists trained pharmacists and ID physicians, pharmacists administered and interpreted
Community hospital [2]	Georgia	Pharmacist driven and interpreted, nursing administered
Community teaching hospital [4]	Michigan	ID physicians, ID pharmacists, pharmacy residents all administered and interpreted
Academic medical center [5]	Maryland	ID Fellows administer and interpret; pharmacists refer patients, provide training, and recommend β-lactam therapy
Public teaching hospital [6]	Texas	Allergists trained pharmacists; pharmacists administered and interpreted
Regional medical center [7]	Tennessee	ID and hospital physicians trained pharmacists; pharmacists administered and interpreted

Cedars Sinai | Bland and Jones Clin Infect Dis 2021 47

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High Priority Populations for Penicillin Allergy Delabeling

Population	Relevant Characteristics
1) Pregnant Women	<ul style="list-style-type: none"> ~25-30% require antibiotics around the time of delivery Allergy label associated with increased Cesarean deliveries, post-op wound complications, longer hospital stays Delabeling during pregnancy considered safe and recommended by the American College of Obstetrics and Gynecology (ACOG)
2) Surgical Patients	<ul style="list-style-type: none"> Allergy label associated with increased surgical site infections
3) Oncology Patients	<ul style="list-style-type: none"> Often require prophylactic antibiotics Higher prevalence of drug allergy labels than the general population Higher risk of developing nosocomial infections and complications from broad-spectrum antibiotics
4) Pediatric Patients	<ul style="list-style-type: none"> Often prescribed beta-lactams for common childhood infections Reactions tend to be mild and rarely (<20%) witnessed by clinicians
5) Military	<ul style="list-style-type: none"> Allergy evaluation programs exist at multiple US Military sites May need antibiotics when deployed and beta-lactams have widespread global availability

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Barriers to Delabeling

- Limited clinical knowledge of drug allergy
- Patient hesitancy
- Provider hesitancy
- Lack of time
- Lack of resources

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Cost

- Delabeling has a favorable cost-benefit ratio
- \$220 per test (\$84 when performed without skin testing)
- Can reduce health care expenses by **\$1,915 per patient per year**



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Summary

- Penicillin causes both immediate and delayed hypersensitivity reactions
- A penicillin allergy label is not benign
 - Associated with worse patient outcomes and antibiotic resistance
- The majority of patients with a penicillin allergy label are not truly allergic
 - Most patients lose their sensitivity after 5-10 years or were mislabeled and never allergic
- Penicillin allergy testing carries minimal risk and is an important part of antimicrobial stewardship
- A drug allergy history and risk stratification are important steps in delabeling
- With proper education and training, both allergists and non-allergists can safely delabel patients with penicillin allergy

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Summary (cont.)

- There are not nearly enough allergists to address even a small fraction of penicillin allergic patients
 - Millions of people (hundreds of thousands in LA County alone)
- Facilities, primary care providers, pharmacists and nurses should proactively delabel patients
- Facility antibiotic stewardship programs can safely delabel patients by:
 - a. Taking a good reaction history (including careful review of past antibiotic administration) AND if needed
 - b. Giving an oral amoxicillin challenge to low risk patients (see LACDPH Penicillin Allergy Delabeling Toolkit: <http://publichealth.lacounty.gov/acd/docs/PenicillinAllergyDelabelingToolkitforHospitals.pdf>) AND if needed
 - c. Performing skin testing for higher risk patients or referring to an allergist

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